REMARKS

Initially, Applicant would like to correct a couple of errors in the Amendment filed May 4, 2005.

At page 18 of said Amendment, the word "barley" is missing before "α-amylase". The relevant paragraph is hereby corrected as shown below.

> As for Lecommandeur et al, such teaches the production of monoclonal antibodies that are capable of binding to barley α-amylase. α-amylase is a protein that comprises in excess of 400 amino acids (425 amino acids for wheat α-amylase and 437 for barley α-amylase). As would be apparent to the skilled artisan, a protein of this size comprises a large number of epitopes. In fact, the instant application shows that antibodies generated while producing the claimed immunoassay were capable of recognizing a large number of epitopes distributed over the length of the amino acid sequences of wheat α-amylase (see, for example, Figure 3). However, an antibody raised against α-amylase may recognize any epitope shown in Figure 3 or any other epitope in the protein. Applicant submits that the ordinary skilled in the art would not have considered that the monoclonal antibodies produced by Lecommandeur et al would have necessarily recognized any of the epitopes recited in the claims rather than any other eiptope in α-amylase. As a consequence, Lecommandeur et al does not describe the essential features of the presently claimed invention.

At page 21 of said Amendment "that" should be inserted between "antibodies" and "were"; and the word "have" has been mistakenly substituted for the word "not". The relevant paragraph is hereby corrected as shown below.

> Moreover, the antibodies that were ultimately determined to be useful in a sandwich ELISA were not those raised against the most immunodominant epitope(s) of α-amylase. As shown in Figure 1, monoclonal antibody 15724 recognized epitopes that were considerably more immunodominant that those

defined in the claims. In contrast to the teaching provided in the specification, a non-inventive skilled artisan at the priority date would have expected monoclonal antibody 15724, against the immunodominant epitope of α-amylase, would ~~not~~ have been most suitable for any immunoassay that detects α-amylase in a test sample. Counterintuitive to conventional wisdom in the art at the priority date, the Applicant found that antibodies against the immunodominant epitope were not necessarily suitable for use in a two-site immunoassay and, in particular, an assay capable of being performed in the field. Applicant found that the antibodies that recognized at least one of three specific epitopes (as defined in Claim 1), that were not as immunodominant as those recognized by monoclonal antibody 15724, were more effective in a two-site assay.

In paragraph 5, on page 2 of the Office Action, the Examiner objects to the Second Supplemental Information Disclosure Statement filed May 4, 2005, on the basis that the cited documents were not provided therewith.

In response, Applicant submits herewith copies of the following documents as part of the Information Disclosure Statement filed simultaneously herewith:

(i) AACC Method 22-05, "Measurement of α-Amylase in Cereal Grains and Flours-Amylazyme Method" (***Exhibit I***);

(ii) Skerrit et al, "Trials show pre-harvest quality test works well in the field", Australian Grain (Jun/Jul 1999) (***Exhibit II***);

(iii) Dines, "Wheat Harvest Cheque $40, 000 higher thanks to sprouting test", Australian Grain (Dec 1999) (***Exhibit III***);

(iv) Ringlund (In: Kruger and LaBerge, Third International Symposium on Pre-Harvest Sprouting

in Cereals, Westview Press, Boulder, CO, USA, 1983, pp 112 to 118) (***Exhibit IV***);

(v) Meredith and Pomeranz (In: Advances in Cereal Science and Technology, Volume VII, American Association of Cereal Chemists, St Paul, MN., pp. 239-320 (1985) (***Exhibit V***); and

(vi) Evaluation of WheatRite™ Test Kits for Sprouted Grain, Report prepared by James S. Psotka of the American Institute of Baking (January 2000) (***Exhibit VI***).

In paragraph 6, on page 2 of the Office Action, the Examiner rejects Claims 25-29 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Specifically, the Examiner contends that the specification fails to provide sufficient written description to demonstrate that Applicant was in possession of a method to determine weather damage in a crop based on the detection of the presence of α-amylase in a sample.

For the following reasons, Applicant respectfully traverses the Examiner's rejection.

As discussed in detail in the above-noted Amendment (see page 11 *et seq.*), Applicant respectfully submits that it was already well established in the art as of the effective filing date of the present application that α-amylase in a cereal crop is associated with weather damage. Applicant cited Meredith et al (*In:* Advances in Cereal Science and Technology, Volume VII, American Association of Cereal Chemists, St Paul, MN, pp. 239-320 (1985)) as providing a comprehensive review of factors involved in pre-harvest sprouting (or weather damage)

wherein the "chief culprit [in weather damage of cereal crops] is the enzyme α-amylase...".

Applicant also relied on the Meredith et al disclosure as describing a number of assays that were in use at or prior to 1985 for determining weather damage in a crop (at page 273 to page 284), of which a majority determine the level of α-amylase in a cereal sample as an indictor of weather damage, such as for example, the Falling Number method (AACC Method 56-81B), the amylograph (AACC Method 22-10) and the rapid visco-analyzer (AACC Method 22-08).

Applicant also relied on the disclosure by Hagberg, *Cereal Chem.*, 37:218-222 (1960), as demonstrating that the Falling Number Assay (AACC Method 56-81B) is considered in the art to predict weather damage (or sprout damage), as described at page 218, third paragraph of Hagberg, such that it is now a standard method for determining weather damage in cereals.

Applicant further relied upon the disclosure by McCleary et al, *J. Cereal Sci.*, 6:237-251 (1987), as demonstrating that the art also recognises α-amylase assay as a standard method for determining weather damage, e.g., in the Ceralpha assay (AACC Method 22-02) which determines α-amylase levels using blocked ρ-nitrophenyl maltoheptaoside (BPNG7).

The Examiner pointed out at paragraph 10 of the Office Action that none of the documents relied upon had been submitted to the U.S. Patent and Trademark Office and, as a consequence, the submissions were deemed non-persuasive.

With the above-noted Information Disclosure Statement, Applicant now submits herewith copies of the above-described documents for consideration by the Examiner, i.e.,:

(i) Meredith et al (In: Advances in Cereal Science and Technology, Volume VII, American Association of Cereal Chemists, St Paul, MN., pp. 239-320 (1985), (***Exhibit V***);

(ii) AACC Method 56-81B, "Determination of Falling Number", (***Exhibit VII***);

(iii) AACC Method 22-08, "Measurement of α-Amylase activity with the rapid visco-analyzer" (***Exhibit VIII***);

(vi) AACC Method 22-10, "Measurement of α-Amylase activity with the amylograph" (***Exhibit IX***);

(vii) Hagberg, *Cereal Chem.*, 37:218-222 (1960) (***Exhibit X***);

(viii) McCleary et al, *J. Cereal Sci.*, 6:237-251 (1987) (***Exhibit XI***); and

(ix) AACC Method 22-02, "Measurement of α-Amylase in plant and microbial materials using the Ceralpha method" (***Exhibit XII***).

In contrast to the Examiner's assertions, Applicant maintains that it was well established prior to the effective filing date of the present application that a method for determining the level of α-amylase in a sample was useful for determining weather damage in a cereal grain or flour derived therefrom.

Applicant respectfully submits that it is also evident from paragraph 3 of the Office Action dated November 4, 2004, that the Examiner accepted that the Falling Number method, which measures α-amylase, was art-recognized for determining

pre-harvest sprouting in a cereal grain. Applicant has also confirmed the efficacy of the inventive process for determining weather damage in cereal crops, by correlating the level of α-amylase detected using the claimed two-site immunoassay with Falling Number in sprouted wheat (see, for example, page 22, line 6 to page 24, line 25, and the data provided in Figures 5A and 5B of the present application).

The present application also demonstrates that the results attained using the claimed two-site immunoassay of the invention correlated with those obtained using the Ceralpha method using sprouted wheat, e.g., at page 25, line 26 to page 26, line 9.

Hence, Applicant respectfully submits that the specification as filed clearly demonstrates that the claimed immunoassay detects sprouted wheat as effectively as the art-recognized Falling Number or Ceralpha assays. Based on the art-recognized utility of α-amylase assays for determining weather damage prior to the effective filing date, it is also clear that the specification contains an adequate written description to demonstrate that Applicant was in possession of a method for determining weather damage as of the effective filing date of the present application.

As for the Examiner's allegation that pre-harvest sprouting may be caused by factors other than weather damage, Applicant respectfully maintains that it is generally accepted in the art that environmental changes, in particular rain, cause per-harvest sprouting (see, for example, Meredith et al (1983) (***Exhibit V***)). Thus, an increase in α-amylase levels or activity is a measure of weather damage or sprouting damage in seed crops. This is evidenced by the large number of assays

used in the art and commercially that detect α-amylase as an indicator of weather damage.

Accordingly, Applicant respectfully submits that the claims have written description support. Thus, Applicant requests withdrawal of the Examiner's rejection.

In addition, in paragraph 7 on page 3 of the Office Action, the Examiner maintains the rejection of Claims 25-29 under 35 U.S.C. §112, first paragraph, as not being enabling for determining weather damage in a plant or crop.

For the following reasons, Applicant respectfully traverses the Examiner's rejection.

As discussed in detail in the above-identified Amendment (see pages 14 *et seq.*), the specification as filed clearly describes methods for producing a sample from a cereal for analysis (for example, at page 22, line 28 to 23, line 9; and page 26, lines 13 to 15), in addition to methods for performing a two-site ELISA (for example, at page 17, line 14 to page 18, line 33; and page 22, line 6 to page 25, line 23); and a two-site immunochromatography assay (for example, at page 25, line 26 to page 27, line 22). These assays were shown to be capable of differentiating between unsprouted and sprouted wheat samples with results attained similar to those observed with the Falling Number method or Ceralpha method. On the basis of these results, Applicant respectfully submits that the instant application provides sufficient description to enable the skilled person to prepare and assay a sample from a cereal to determine the level of α-amylase in the sample and to determine whether or not the sample comprises pre-harvest sprouted (or weather damaged) cereal.

In support of the use of the immunochromotography assay as described in the present application for assessing weather

damage in a variety of cereal crops, Applicant relied in its previous submissions upon the disclosure by Skerrit et al, *Crop Sci.*, 40:742-756 (2000). Applicant submitted that Skerrit et al determined the level of α-amylase in an initial set of 14 grain samples from Australia with varying degrees of weather damage (i.e., having Falling Number between 100s and 403s) and 36 samples subjected to controlled wetting (i.e., having Falling Number between 85s and 423s) and concluded that the immunochromatography method produced results that closely correlated with the Falling Number results (linear regression r^2 = 0.954 or r^2 = 0.970), as discussed at page 746, right-hand column, and shown in Figures 3A and 3B of Skerrit et al. Applicant also relied upon Skerrit et al as showing that the immunochromatography data were reproducible with little within or between assay variation (as discussed at page 746, right-hand column of Skerrit et al).

The Examiner pointed out at paragraph 10 of the Office Action that a copy of the Skerrit et al publication was not filed in the U.S. Patent and Trademark Office and, as a consequence, these submissions were deemed non-persuasive.

Applicant now submits herewith a copy of the following document for consideration by the Examiner as part of the Information Disclosure Statement filed simultaneously herewith:

(i) Skerrit et al, *Crop Sci.*, 40:742-756 (2000), (***Exhibit XIII***).

Applicant respectfully maintains that the immunochromatography assay used in Skerrit et al (2000) employs the methodology described in the instant application. This assay has been clearly shown to be useful for determining

the level of weather damage in a cereal sample. Proceeding on this basis, Applicant submits that the instant application clearly enables the production of an assay that determines weather damage in a cereal crop.

Accordingly, Applicant respectfully submits that the claims are enabled by the present specification. Thus, Applicant requests withdrawal of the Examiner's rejection.

In paragraph 9, on page 4 of the Office Action, the Examiner rejects Claim 1, 3-14 and 23-30 under 35 U.S.C. §102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. §103 as being obvious over LeCommandeur et al.

The Examiner notes Applicant's argument that LeCommandeur et al does not specifically teach that it's α-amylase specific monoclonal antibodies bind to either a first or second epitope comprising one or more amino acid sequences selected from the group consisting of SEQ ID NOs:1, 2 and 3. However, the Examiner contends that this argument is not persuasive since LeCommandeur et al teaches that the monoclonal antibodies thereof bind to different epitopes on barley α-amylases and that the present invention detects α-amylases from barley. Hence, the Examiner concludes that since it appears that the identical analyte is being detected in LeCommandeur et al, the invention is anticipated thereby.

For the following reasons, Applicant respectfully traverses the Examiner's rejection.

Lecommandeur et al merely teaches the production of monoclonal antibodies that are capable of binding to barley α-amylase. With respect, α-amylase is a protein that comprises in excess of 400 amino acids (425 amino acids for wheat α-amylase and 437 for barley α-amylase). As would be apparent to the skilled artisan, a protein of this size

comprises a large number of epitopes. In fact, the instant application shows that antibodies generated while producing the claimed immunoassay were capable of recognizing a large number of epitopes distributed over the length of the amino acid sequence of wheat α-amylase (see, for example, Figure 3). Applicant respectfully submit that an antibody raised against α-amylase may recognize any epitope shown in Figure 3 or any other epitope in the protein. Applicant submits that the ordinary skilled person would not have considered that the monoclonal antibodies produced by Lecommandeur et al, would have necessarily recognized any of the epitopes recited in the claims rather than any other epitope in α-amylase. As a consequence, Lecommandeur et al, does not necessarily describe the essential features of the presently claimed invention.

In response to the Examiner's allegation that the epitopes of SEQ ID NOs:1-3 are inherent in the barley α-amylase sequences, Applicant submits, as part of the Information Disclosure Statement filed simultaneously herewith, ***Exhibit XIV***, a copy of NCBI database extracts showing the amino acid sequences of two high pI forms of barley α-amylase, i.e., Accession Nos. CAA33298 and CAA33299. Applicant respectfully submits that it is clear from the barley sequences that the closest identities to SEQ ID NOs:1-3 of the present application are as follows:

SEQ ID NO: 1:

wheat:	IDRLVSIRTRGQIHS	(SEQ ID NO: 1)
barley1:	IDRLVSvRTRhgIHn	(residues 358-372 of Accession No. CAA33298)
barley2:	IDRLVSIRTRqgIHS	(residues 360-374 of Accession No. CAA33299)

SEQ ID NO: 2:

wheat:	CRDDRPYADG	(SEQ ID NO: 2)
barley1:	CRDDRPYADG	(residues 148-157 of Accession No. CAA33298)
barley2:	CRDDRPYpDG	(residues 148-157 of Accession No. CAA33299)

SEQ ID NO: 3:

wheat:	VNWVNKVGGS	(SEQ ID NO: 3)
barley1:	VNWVdKVGGk	(residues 253-262 of Accession No. CAA33298)
barley2:	VNWVNKVGGS	(residues 255-264 of Accession No. CAA33299)

Applicant respectfully submits that neither barley sequence comprises more than one of the epitopes recited in Claim 1 of this application. The barley 1 sequence (Accession No. CAA33298) only comprises the sequence set forth in SEQ ID NO:2 in its entirety, and the barley 2 sequence (Accession No. CAA33299) only comprises the sequence set forth in SEQ ID NO:3 in its entirety. In contrast, Claim 1 clearly requires the α-amylase protein detected by the two site immunoassay to comprise at least two of the three recited epitopes.

Applicant respectfully submits that to maintain the allegation of inherency of disclosure in LeCommandeur et al, it would be necessary to demonstrate as a minimum that two or more epitopes in any barley isoenzyme are precisely the same as those recited in the claims. This is because the two-site immunoassay of the invention binds α-amylase, e.g., to a solid substrate by binding of a first epitopic determinant in the protein to a first antibody. The bound protein is then detected by binding a second antibody to a second epitopic determinant in the protein. Thus, binding and detection will only occur if two epitopic determinants are present. In this case, neither high pI barley alpha-amylase protein contains two or three epitopic determinants recognized by the monoclonal antibodies that bind to wheat α-amylase. Hence, the Examiner is not correct in asserting that the invention as claimed inherently lacks novelty over LeCommandeur et al.

Moreover, as the barley high pI α-amylase proteins do not contain at least two epitopes that are also present in the wheat enzyme, it is clearly not possible to conclude that

LeCommandeur et al would actually provide cross-reaction with the wheat α-amylase protein. It is not sufficient for the Examiner to assert that this might be the case, particularly in view of the differences between the barley and wheat isoenzymes as discussed *supra,* and the fact that single amino acid differences may modify antigenicity and antibody binding. As stated previously, LeCommandeur et al merely mentions that ELISA type assays might, not would, be useful in detecting α-amylase levels in wheat but does not indicate how any specific epitope can be used to perform such a method. Thus, the disclosure is merely an invitation to experiment and does not render obvious a two-site immunoassay that comprises antibodies that recognize two specific epitopes.

Moreover, as noted in the above-identified Amendment (see page 19 *et seq.*), the description at page 19, lines 3-9, of the subject specification makes it abundantly clear that not all antibodies raised against α-amylase are capable of detecting α-amylase in a sandwich (i.e. two-site) ELISA. Antibodies that were not useful in a sandwich ELISA were found to bind to different epitopes to those defined in the claims (page 20, lines 30-31, and Figure 3). In fact, the antibodies that were ultimately determined to be useful in a sandwich ELISA were not those raised against the most immunodominant epitope/s of α-amylase. As shown in Figure 1, monoclonal antibody 15724 recognized epitopes that were considerably more immunodominant than those defined in the claims. In contrast to the teaching provided in the specification, a non-inventive skilled artisan at the priority date would have expected that monoclonal antibody 15724 against the immunodominant epitope of α-amylase would have been most suitable for any immunoassay that detects alpha-amylase in a test sample. Counterintuitive

to conventional wisdom in the art at the priority date, Applicant found that antibodies against the immunodominant epitope were not necessarily suitable for use in a two-site immunoassay and, in particular, an assay capable of being performed in the field. Applicant found that antibodies that recognised at least one of three specific epitopes (as defined in the Claim 1), that were not as immunodominant as those recognised by monoclonal antibody 15724, were more effective in a two-site assay.

Accordingly, Applicant respectfully submits that the present invention is not taught or suggested in LeCommandeur et al, and thus request withdrawal of the Examiner's rejection.

In view of the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 290-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: November 16, 2005